accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

Status of the Claims.

Claims 1-8 are pending with entry of this amendment, no claims being cancelled and no claims being added herein. Claim 1 is amended herein. This amendments introduce no new matter. Support is replete throughout the specification (*e.g.*, in the examples, in the claims as filed, *etc.*).

Information Disclosure Statement.

The Examiner alleged that the Information Disclosure Statement (form 1449) failed to comply with 37 C.F.R. §1.98(a)(3) because reference A35 allegedly provided only a sequence listing without any explanation as to how the sequence is relevant to the instant application. A copy of this reference provided by the Examiner, appears to be missing the accompanying descriptive information. Accordingly, Applicants provide, once again, a PTO 1449 form with accompanying reference A35 including the apparently missing information.

35 U.S.C. §112, First Paragraph.

Claims 1-8 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled for a method of screening for a disease state associated with cirrhosis of the liver in a mammal. In particular, the Examiner alleged that because YKL-40 levels are elevated in patients with rheumatoid arthritis or other joint diseases and in breast cancer, YKL-40 level cannot be related to one specific disease in any mammal. The Examiner, however, alleged that the YKL-40 level can be treated to a disease, *i.e.*, alcoholic cirrhosis of the liver, in a patient suspected of having such a disease.

Accordingly, the Examiner recommended amending claim 1 as follows:

> 1. A method of screening for the presence of **[for a disease state associated with]** alcoholic cirrhosis of the liver which is associated with degradation of connective tissue containing YKL-40 in a **[mammal]** **patient suspected of having alcoholic cirrhosis of the liver**, said method comprising:
>
> measuring the level of YKL-40 in a biological sample of the **patient** **[mammal]**; and

comparing the level to that of a normal, healthy mammal, wherein a statistically significant difference indicates the presence of said **[disease state] alcoholic cirrhosis of the liver in said patient.**

Applicants appreciate the Examiner's constructive suggestion. However, Applicants believe the Examiner's proposed amendment is too limiting. Instead, Applicants have amended claim 1 herein as follows:

1. A method of screening for **the presence of [a disease state associated with]** cirrhosis of the liver in a mammal, said method comprising measuring the level of YKL-40 in a biological sample of the mammal and comparing the level to that of a normal, healthy mammal, wherein a statistically significant difference **is an indicator for the presence of cirrhosis of the liver.[indicates the presence of said disease state]**.

Applicants note that the amendment to the first line is comparable to the Examiner's recommendation.

With respect to the "patient suspected of having alcoholic cirrhosis of the liver" language proposed by the Examiner, Applicants note that the patient need not be suspected of having cirrhosis of the liver. To the contrary, **even where there is no suspicion of cirrhosis of the liver, in light of the teaching provided in the present specification, an elevated YKL-40 level will lead one of skill to consider the possibility that the assayed mammal does suffer from cirrhosis of the liver.** There is thus, no reason to limit the claimed methods to "a patient suspected of having alcoholic cirrhosis of the liver".

spec is not so clear as to teach this →

Because, in light of the teaching provided in the present specification, an elevated YKL-40 level will lead one of skill in the art to consider that the subject mammal has cirrhosis of the liver, elevated YKL-40 is **an indicator of cirrhosis**. Like any other assay for a disease state, the assays of this invention are typically performed in the context of a differential diagnosis. As clarified by the amended claim, the assay provides an **indicator** (indication), in this instance, of cirrhosis and conformation of the disease state is routine to those in the medical profession.

Enablement does not require that the claimed assay provide an completely unambiguous determination of the presence of cirrhosis. The Examiner will appreciate that no diagnostic assay provides unequivocal results. To the contrary all assays provide a certain incidence,

e.g. of false positives. Nevertheless, such assays are useful because they are performed in the context of a differential diagnosis and provide one indication of the condition in question.

The assay of this invention is similar. Moreover, to emphasize/clarify this point, as indicated above, claim 1 is amended herein to recite: ". . . wherein a statistically significant difference **is an indicator for the presence of cirrhosis."**

The claimed invention is thus commensurate in scope with the disclosure and the examples provided therein, and no undue experimentation is required to practice the claimed method. Accordingly, the rejection of claims 1-8 under 35 U.S.C. §112, first paragraph, should be withdrawn..

Obviousness-Type Double Patenting.

Claims 1-8 were rejected under the judicially created doctrine of obviousness-type double patenting in light of claims 1-25 of U.S. Patent 5,935,798. Applicants respectfully traverse.

The Examiner is reminded that a double-patenting rejection is essentially an obviousness rejection **in light of the claims** of one or more earlier patents. As stated by the Federal Circuit:

> A double patenting of the obviousness type rejection is "analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. §103," except that **the patent principally underlying the double patenting rejection is not considered prior art**. In *re Longi,* 225 USPQ 645 (Fed. Cir. 1985) *n.4, citing In re Braithwaite* 154 USPQ 29, 34 (CCPA 1967)

The inquiry is whether or not the claimed invention is patentably distinct (nonobvious) from the cited claims and references and this is evaluated under the body of law pertaining to the analysis of obviousness under 35 U.S.C. §103(a).

An obviousness rejection requires a teaching or suggestion to modify the references in the manner indicated by the Examiner. As stated by the Court of Appeals for the Federal Circuit:

> Our case law makes clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references. See Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617. **"Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight."** Id.

> [emphasis added] *Ecolochem, Inc. v Southern-California Edison Company,* __ USPQ2d ___ (Fed. Cir. 2000)
>
> * * *
>
> The mere fact that the prior art may be modified in the manner suggested by the Examiner **does not** make the modification obvious unless the prior art suggested the desirability of the modification. [emphasis added] *In re Fritch*, 23 USPQ 2d 1780, 1783-1784 (Fed. Cir. 1992)

The presently pending claims incorporate a limitation not recited in the claims of the '798 patent. In particular, presently pending claim 1 recites:

> 1. A method of screening for the presence of **cirrhosis of the liver** in a mammal, said method comprising measuring the level of YKL-40 in a biological sample of the mammal and comparing the level to that of a normal, healthy mammal, wherein a statistically significant difference **is an indicator for the presence of cirrhosis of the liver**. [emphasis added]

The claims of the '798 patent generically refer to 1. "a method for screening for the presence of a disease state which is associated with degradation of connective tissue containing YKL-40", but fail to teach or suggest a method of screening for the presence of **cirrhosis of the liver**.

The Examiner has failed to articulate with particularity a teaching or suggestion of a method of screening for the presence of **cirrhosis of the liver**. The claims of the '798 patent are silent respect to cirrhosis of the liver.

The claims of the '798 patent simply fail to teach or suggest all the elements of the presently claimed invention. Accordingly, the present invention is not obvious in light of these claims and the obviousness-type double patenting rejection should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/215,077 WITH ENTRY OF THIS AMENDMENT

In the specification:

[Not Applicable]

In the claims:

1. A method of screening for **the presence of [a disease state associated with]** cirrhosis of the liver in a mammal, said method comprising measuring the level of YKL-40 in a biological sample of the mammal and comparing the level to that of a normal, healthy mammal, wherein a statistically significant difference **is an indicator for the presence of cirrhosis of the liver.[indicates the presence of said disease state]**.

APPENDIX B

CLAIMS PENDING IN USSN 09/215,077 WITH ENTRY OF THIS AMENDMENT

1. A method of screening for the presence of cirrhosis of the liver in a mammal, said method comprising measuring the level of YKL-40 in a biological sample of the mammal and comparing the level to that of a normal, healthy mammal, wherein a statistically significant difference is an indicator for the presence of cirrhosis of the liver.

2. The method of claim 1, wherein the amount of YKL-40 in said sample is measured using an immunoassay.

3. The method of claim 2, wherein the immunoassay is a competitive immunoassay.

4. The method of claim 3, wherein the immunoassay utilizes a detectable label selected from the group consisting of radioisotopes, enzymes, fluorescent molecules, chemiluminescent molecules, bioluminescent molecules, and colloidal metals to measure YKL-40.

5. The method of claim 1, wherein said mammal is a human.

6. The method of claim 2, wherein the immunoassay uses a polyclonal antibody to measure YKL-40.

7. The method of claim 2, wherein the immunoassay uses a monoclonal antibody to measure YKL-40.

8. The method of claim 1, wherein said sample is selected from the group consisting of blood, plasma, and serum.

9. Antibodies that specifically bind to a YKL-40.

10. The antibodies of claim 9, wherein said antibodies are polyclonal antibodies produced by immunization of a non-human mammal.

11. The antibodies of claim 9, wherein said antibodies are monoclonal antibodies produced by hybridomas formed from cells taken from a non-human mammal.

12. A kit for use in the detection of a disease state in a mammal associated with degradation of connective tissue, said kit comprising a YKL-40 antibody.

13. The kit of claim 12, wherein said disease state is selected from the group consisting of an inflammatory or degenerative joint disease, cirrhosis of the liver, and metastatic cancer.

14. The kit of claim 12, wherein said YKL-40 antibody is a polyclonal antibody.

15. The kit of claim 12, wherein said YKL-40 antibody is a monoclonal antibody.

16. The kit of claim 12, further comprising immunoassay reagents.

17. The kit of claim 12, further comprising a detectable label.